

Summary report on the

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# Regional meeting of the directors of national influenza laboratories in the Eastern Mediterranean Region

Casablanca, Morocco  
16–17 November 2019



REGIONAL OFFICE FOR THE

World Health  
Organization

Eastern Mediterranean

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## **1. Introduction**

The WHO Regional Office for the Eastern Mediterranean held a two-day meeting in Casablanca, Morocco, on 16–17 November 2019, of the directors of national influenza centres (NICs) and other national influenza laboratories in the WHO Eastern Mediterranean Region, as well as representatives from WHO collaborating centres and other experts, to discuss issues, challenges and solutions for the laboratory surveillance of seasonal, avian and other influenza viruses of pandemic potential. The meeting was attended by directors of NICs and other national laboratories from 22 countries.

The meeting's objectives were to:

- discuss current challenges in detection and characterization of influenza viruses and share new laboratory techniques and methodologies for influenza virus detection and characterization;
- critically analyse and evaluate current knowledge on influenza virology, WHO tools, detection and characterization methods for influenza virus, approaches to implementing antigenic and genetic characterization and anti-viral resistance surveillance, and external quality assessments; and
- discuss ways to strengthen biosafety and biosecurity, reporting, virus-sharing and data utilization in the Region.

The meeting provided an opportunity to review the functioning of NICs in the Region, strengthen collaboration and information-sharing among countries, and identify needs, creative solutions and best practices in strengthening/maintaining laboratory capacity for the detection of influenza viruses. Based on the discussions, recommendations were developed for countries, WHO and other stakeholders.

## **2. Summary of discussions**

The meeting was inaugurated by Dr Abdinasir Abubakar, Acting Programme Area Manager, Infectious Hazard Management, WHO Regional Office for the Eastern Mediterranean, who outlined the critical role of NICs in regional and global influenza surveillance and response. Dr Abubakar hailed the efforts of NICs in the detection and identification of influenza viruses using real-time polymerase chain reaction (RT-PCR), influenza virus isolation and other diagnostic methods. He emphasized the importance of timely and consistent data reporting to FluNet for the global system of influenza surveillance and the need to maintain the quality of the data uploaded. Dr Abubakar called on NIC managers to adopt best practices in laboratory management, make biosafety and biosecurity a priority, and share experiences and expertise.

### *Current situation of NICs and national influenza laboratories in the Region*

NICs are institutions responsible for the laboratory surveillance of influenza. They collect virus specimens in their country and perform preliminary analysis, and ship representative clinical specimens and isolated viruses to WHO collaborating centres for advanced antigenic and genetic analysis. The results form the basis for WHO recommendations on the composition of influenza vaccine each year, as well as relevant risk assessment activities of WHO. They are designated by ministries of health and formally recognized by WHO for participation in the WHO Global Influenza Surveillance and Response System (GISRS).

As of November 2019, the Region has 17 NICs in 16 countries. Globally, there are 146 NICs in 123 countries, including six WHO collaborating centres (none of which are in the Region).

The process of recognition as an NIC involves an on-site assessment by WHO using a standardized laboratory assessment tool based on WHO (recently updated) terms of reference (ToR) and basic standards for laboratory quality. An NIC recognized by WHO maintains direct working relations with the WHO Global Influenza Programme and WHO collaborating centres for reference and research on influenza and should comply with the ToR for NICs. WHO monitors compliance with the ToR and reassesses the performance of each recognized institution annually to determine whether it can retain its NIC status.

A WHO review of the performance of NICs in 2018 classified them into two categories according to their performance: those partially compliant with the updated ToR that retain their status as a recognized NIC but need support to achieve proficiency status (category 1); and those fully compliant with the updated ToR and categorized as proficient (category 2). Three NICs from the Region were placed in category 2 and 12 laboratories in category 1. One NIC has been inactive during recent years.

The number of NICs from the Region participating in the External Quality Assessment Project (EQAP) for the detection of influenza viruses by PCR increased from two laboratories in 2007 to 19 in 2018. The percentage of NICs scoring fully-correct results for the detection of influenza virus by PCR increased from 50% in 2007 to 100% in 2017; however, this dropped to 70.6% in 2018, although the number of countries participating in the EQAP increased in 2018. In 2019, 19 influenza laboratories participated, with a regional score of 88.9%.

In 2018, eight NICs in the Region participated in the second External Quality Assessment (EQA) to assess the isolation and identification of influenza viruses using cell culture techniques. For virus isolation, 5/8 obtained correct results for  $\geq 10/15$  samples. Regarding virus identification, 6/8 laboratories obtained correct results for  $\geq 10$  EQA

samples. In 2019, the WHO Regional Office conducted a second MERS-CoV EQA, with 20 laboratories in the Region returning panel results. The laboratories demonstrated good proficiency in detecting MERS-CoV, with 100% of laboratories reporting correct results for all specimens.

Overall, EQA results show a general improvement in the technical ability of network laboratories, but also identify topics for future training and monitoring. Laboratories with low performance in the EQA receive training and technical support for corrective action.

### *The Nagoya Protocol, virus-sharing and RSV surveillance*

In a presentation on GISRS, the expectations for NICs were described, including in virus detection and isolation and sampling quality improvement. GISRS requirements for virus sharing, data reporting to Flunet and communication were outlined. An update was provided on WHO efforts to support stakeholders in monitoring the evolution of influenza virus circulation, including on policy and the Nagoya Protocol. The Protocol faces several challenges, including a lack of legal clarity, transparency and understanding in some countries, and delays in working with seasonal influenza viruses in countries. Urgent action has been identified to improve the sample-sharing process in line with the Protocol and GISRS ToR.

An overview of the WHO global respiratory syncytial virus (RSV) surveillance project was presented, including its goals, phases, operation (including algorithm testing and case definition) and achievements so far. Phase II is currently underway. The projects activities should be embedded in the national (influenza) surveillance process, taking advantage of available technical resources for influenza surveillance.



*Laboratory-based influenza surveillance sustainability, challenges and the way forward*

In order to achieve the goals of GISRS, NICs need to maintain capacities specified in the International Health Regulations (IHR), 2005. An effective laboratory capacity-building action plan is critical for real-time detection of currently-existing influenza viruses or any emerging or re-emerging respiratory viruses. A capacity-building process needs to be integrated within the system at country level. A plan with a timeline for specific actions and long-term financial commitment from the ministry of health is the best guarantor of the sustainability of influenza surveillance. This is achievable through good communication of the programme's outputs to stakeholders and the public. Several success stories exist as models, including in China, Mongolia, Philippines and Thailand.

*Detection and characterization of influenza viruses in the Region*

The NIC directors of Bahrain, Egypt, Islamic Republic of Iran, Lebanon, Pakistan and Tunisia provided an overview of the implementation of national influenza virological surveillance systems and challenges in their respective countries. They presented their laboratories' capacities, activities, testing algorithms, flow capacity, statistics and achievements.

Regarding challenges and limitations, country representatives reported shortages of reagents, logistical issues, rapid turnover of staff, difficulties in interpreting genetic characterization from WHO collaborating centres, the need to build the capacity of human resources, and data-sharing and communication issues between subnational laboratories and national public health laboratories.

*Nucleic acid detection and sequencing of epidemic and zoonotic influenza viruses*

Most NICs have the capability to carry out virus detection and subtyping using molecular procedures. The importance of virus characterization during the season and outbreaks was highlighted. An overview was given of the RT-PCR assays developed by CDC for detection of influenza A and B viruses and to rapidly determine influenza A virus subtype or influenza B virus lineage in clinical samples. The suite of CDC RT-PCR kits for detection and initial characterization of both epidemic/seasonal viruses and zoonotic subtypes that represent pandemic threats, and their availability via the International Reagent Resource, were discussed. The influenza surveillance testing algorithm, the difference between untyped and unsubtypeable influenza viruses, and the reasoning behind the rules for immediate sharing of any unsubtypeable virus with WHO collaborating centres were explained. The new sequencing approach using the next generation sequencing (NGS) algorithm and its added value for virus characterization, and an innovative NGS tool from Oxford Nanopore Technologies for deployment in the field during outbreak response, were presented.

*Antigenic and molecular characterization of influenza viruses from the 2018–2019 influenza season and prospects for the upcoming season*

The antigenic and genetic evolution of influenza types A and B since February 2019 and how the 2019–2020 influenza composition for the southern hemisphere was determined were described. Nearly all A(H1N1)pdm09 viruses had haemagglutinin (HA) gene sequences that belonged to phylogenetic clade 6B.1, represented by A/Michigan/45/2015.

Some viruses fell into a group that had substitutions at residues 156 that were antigenically different from the majority, but these viruses have

limited circulation of antigenic variants. It was recommended that vaccines for use in the 2020 southern hemisphere influenza season contain an A/Brisbane/02/2018 (H1N1)pdm09-like virus, the same as in February for the northern hemisphere. Phylogenetic analysis of A(H3N2) viruses collected from February to August 2019 showed considerable genetic diversity: 3C.3a resurgence not continued, 3C.2a2 viruses declined considerably, and two divisions had occurred in 3C.2a1b: 128 and 135 loss of CHO at both sites and T131K.

Three antigenically distinguishable groups were reported: 3C.3a, 3C.2a2, and 3C.2a1b and a new genetic group in 3C.2a1b without CHO that appear antigenically different from other 3C.2a1b viruses. Therefore, it was recommended that quadrivalent influenza vaccines for use in the 2020 southern hemisphere contain an A/South Australia/34/2019 (H3N2)-like virus (clade 3C.2a1b). Among influenza B/Victoria lineage viruses analysed, multiple genetically and antigenically distinct B/Victoria lineage viruses co-circulated. The most common globally belonged to subclade 1A(D3)B. A huge decline in B/Yamagata lineage viruses over the last 16 months has been observed. Several substitutions occur in multiple locations (D229N; D232N +CHO) but with no change in antigenic properties. It was recommended that vaccines for use in the 2020 southern hemisphere influenza season contain in the quadrivalent a B/Washington/02/2019-like (B/Victoria lineage) virus with a triple deletion virus, and a B/Phuket/3073/2013-like (B/Yamagata lineage) virus the same as the northern hemisphere composition.

### *NGS implementation at NICs*

NGS as a high-throughput sequencing technology for the identification within-sample variants presents a low percentage. It reduces the turnaround time to the point where sequence information can be used in “real time” to support public health measures for control of outbreaks.

Choosing which platform to use can be difficult, but it comes down to deciding which of the following factors are most important: amount of sequence, read length, price, accuracy, expertise and application flexibility. A guideline for purchasing NGS technologies and decision-making will be released very soon by WHO. Considerations to take into account for their acquisition include the number of samples, the type of technology, capacity for data storage, sequence assembly and analysis, library construction and human resources.

*Influenza virus-sharing in the Region: what has been achieved so far and ways to improve virus-sharing.*

The contribution of influenza laboratories and NICs from the Region to global influenza surveillance is significant, with considerable variation in numbers of specimens being shared by individual countries. There are existing bilateral cooperative agreements between countries in the Region and CDC for capacity-building and technology transfer to routinely identify, diagnose and respond to seasonal and pandemic influenza.

However, there has been a decline in data-sharing by countries, as illustrated by NIC participation statistics, including number of shared samples and sharing timelines. Timely virus isolation and sharing of isolates and/or samples is one of the most important duties for all NICs and national influenza laboratories, along with data-sharing. Issues were noted with the timeliness of sample-sharing to allow analysis before WHO influenza vaccine composition meetings (VCMs), and/or sharing specimens with “old” collection dates not relevant to the upcoming VCM.

Several improvement tracks have been identified:

- ensure collection of good clinical specimens through training of medical personnel and their transport using the appropriate viral

transport medium, containers, labelling and a cold-chain of 4°C short-term, and at least -70°C long-term, with as few freeze/thaw steps as possible;

- ensure rapid cold-chain shipments to NICs/national laboratories for timely testing (and preliminary characterization) and availability for sharing with WHO collaborating centres for detailed characterization;
- ensure shipping of unsubtypeable samples as soon as possible; and
- ensure correct filling of the shipping form and the use the right destination address (to the Francis Crick Institute, London, UK).

*Integration of RSV and other emerging pathogens into the influenza platform*

A WHO pilot initiative in Egypt to assess the feasibility of establishing RSV surveillance using the existing GISRS platform was presented. The pilot surveillance system started in January 2016 and included five selected sentinel sites. Annual seasonality of RSV in Egypt, a sub-tropical country, was observed and RSV activity was found to peak in the cooler season. RSV positivity is predominant in the  $\leq 2$  years age group, and a fatal outcome (mortality rate) is most commonly found in RSV-positive children  $\leq 2$  years (1.8%). Egypt decided to maintain laboratory-based surveillance for RSV and currently participates in WHO RSV surveillance phase 2 (2019–2021) for better understanding of acute respiratory infections and prevention and control strategies.

The experiences of Jordan and Morocco in using the commercial multiplex RT-PCR, FTD Respiratory pathogens 21 kit (Fast Track Diagnosis, Luxembourg) to study the etiology of respiratory pathogens in patients with influenza-like illness (ILI) and severe acute respiratory infection (SARI) were presented.

The results of a study undertaken in Saudi Arabia in collaboration with WHO to investigate the etiology of respiratory pathogens in patients presenting with SARI during the 2018 Hajj season were presented. Out of 132 SARI specimens negative for influenza, 67 were positive for respiratory viruses. Rhinoviruses were most represented, but this may not be significant because rhinoviruses can persist in people long after infection has cleared, and so may not be relevant to current infection. Some of the patients had multiple viruses, which is not unusual (25/67 were positive for more than one virus).

The experiences of Kuwait, Qatar and United Arab Emirates with the MERS-CoV/influenza testing algorithm were shared. While Qatar tests all SARI/ILI samples for a panel of 21 viruses, including MERS-CoV, Kuwait only tests for MERS-CoV in suspected cases. United Arab Emirates tests ILI samples for influenza, SARI samples for influenza, MERS-CoV and RSV, and SARI ICU admissions receive a respiratory MDx panel test (Allplex) and are tested for MERS-CoV if negative. Qatar and United Arab Emirates reported issues with the GeneXpert assay, which misses a high number of influenza H1N1pdm and H3N2. It was confirmed that this test is behind the “evolutionary curve” of H1pdm09 viruses and A(H3N2), which is why the assay did not identify some influenza viruses.

Presentations were made on the experiences Afghanistan, Iraq and Syrian Arab Republic in developing respiratory and emerging infectious disease laboratory surveillance in compromised security situations using the influenza platform and the challenges faced, including lack of commitment from ministries of health, security instability, lack of resources, long delays in receiving influenza kits from the Influenza Reagent Resource and staff departures.

*Influenza preparedness*

The laboratory component of national influenza pandemic preparedness plans and national action plans for health security in the Region were outlined and how the two plans are linked. The importance of the laboratory component of both plans was highlighted, as was the special attention needed for biosafety, which scored low(est) during the joint external evaluations (JEE). Participants, most of whom were not aware of the plans, were recommended to locate and familiarize themselves with their country's JEE report, national influenza pandemic preparedness plans and national action plans for health security, and to participate in their update, implementation and rehearsal using WHO guidance.

**3. Recommendations***To Member States*

1. NICs recognized by WHO should maintain direct working relations with GISRS and should comply with the updated NIC ToR.
2. NICs belonging to category 1 (partially compliant with WHO ToR) should work closely with the WHO Regional Office to fill the gaps revealed by the WHO review of NIC capacities.
3. NICs/national influenza laboratories should continue to strengthen/maintain laboratory capacity for the detection of influenza viruses and ensure laboratory quality through participation in external quality assessment (EQA).
4. NICs/national influenza laboratories should ensure safe and accurate diagnostic test results by strengthening their quality management system, including for biosafety and biosecurity.
5. NIC/national influenza laboratories should enhance their core capacities to support the national influenza preparedness and

response plan and to respond to other emerging and re-emerging seasonal and novel influenza viruses.

6. NICs/national influenza laboratories should familiarize and actively involve themselves in the JEE, national influenza pandemic preparedness plans and national action plans for health security.

*To WHO*

7. Continue to conduct periodic (every 2–3 years) performance reviews of NICs to ensure that the regional network continues to work effectively and continue to support all national influenza laboratories to comply with ToR for NIC core responsibilities.
8. Continue to provide Member States with guidance, technical support, training and tools for strengthening influenza diagnosis, quality management and biorisk management systems.
9. Continue encouraging NICs/national influenza laboratories to test for other respiratory viruses.
10. Provide Member States with guidance, technical support, training and tools for NGS, phylogenetic analysis and antiviral susceptibility monitoring activities.
11. Encourage NICs to engage with and participate in the Nagoya Protocol and identify an access and benefit-sharing (ABS) focal person.



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